RESEARCH STUDIES

Intensive phase efficacy of injected drugs – isoniazid and rifampicin in the treatment of patients with lung tuberculosis and hepatobiliary pancreatic comorbidities

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Abstract

Background: One of the most important tuberculosis control action represents the effective anti-tuberculosis treatment. The standard regimens are associated with high level of side effects, especially at patients with hepatobiliary and pancreatic co-morbidities.

Material and methods: There were studied clinical and laboratory indices of a total number of 60 new pulmonary tuberculosis cases, with proved hepatobiliary and pancreatic comorbidities, distributed in the 1st study group, consisted of 30 patients treated with the standard anti-tuberculosis treatment, all drugs being administrated orally and the 2nd control group, consisted of 30 patients, treated with the standard anti-tuberculosis treatment with injected forms of first line anti-tuberculosis drugs isoniazid and rifampicin.

Results: The clinical improvement of the patient's general state under the influence of intravenous use of isoniazid and rifampicin was confirmed by a lower expressiveness of intoxication and bronchopulmonary syndroms, as well as by a better radiological dynamics and higher rate of microscopic convertion at the end of intensive phase of the tuberculosis treatment. Biochemical disturbances due to tuberculosis treatment were less evident at the patients treated with intravenous isoniazid and rifampicin, confirmed by a better rehabilitation of mathematic indices of endogenous intoxication.

Conclusions: Assessing the differences between the clinical and laboratory tolerance of tuberculosis drugs according to the way of administration, it was proved the importance of individualization of the standard treatment at patients with hepatobiliary and pancreatic disorders by intravenous use of isoniazid and rifampicin in intensive phase of the treatment, for improving the therapeutical effectiveness.

Key words: tuberculosis, comorbidities, treatment, injected drugs.

Background

One of the most important tuberculosis control action represents the effective anti-tuberculosis treatment that is the most important tool for interrupting the epidemiological chain of infectious transmission. As well as, other aims of specific treatment represent: the restoring of health, quality of life and patient's productivity, prevention of death due to tuberculosis (TB) and relapse, and prevention of acquiring of drug resistance [9, 15]. According to World Health Organization (WHO) Treatment Guidelines anti-TB drugs are classified into five groups, based on evidence of efficacy, potency and drug class. First-line anti-TB drug, also called essential first-line drugs, are recommended in a four-drug regimen, containing: isoniazid, rifampicin, pyrazinamide, etambutol for the treatment of drug-susceptible TB in the frame of so-called Directly Observed Therapy (DOT) [15]. DOT by definition means watching the patients swallowing each dose of anti-TB drugs [9]. In the frame of actually used Directly Observed Treatment Short Course Chemotherapy strategy (DOTS), the anti-TB treatment is standardized, meaning that all patients receive the same regimens, being included in well-defined groups. The standard treatment has advantages over individualized treatment by preventing prescription errors, appropriate appreciation of drug needs, distribution and monitoring. By economical mean, standard treatment shows reduced costs and permits a comparable evaluation of treatment outcomes [9]. For standard treatment, the patients are grouped according the prior anti-TB treatment course: new patients are the cases who have no history of a prior TB treatment or who received less than 1 month the anti-TB drugs and previously treated patients, includes patients who relapsed, who failed the prior treatment and patients returned after default. The total duration of the drug susceptible treatment at new patients is 6 months and consists of intensive phase, lasting 2 months and continuous phase (ambulatory phase), lasting 4 months. During the intensive phase 4 first-line TB drugs (IHN, RIF, PZA, EMB) are recommended and during the continuous phase 2 drugs are used (IHN, RIF). The main form of first line TB-drug administration is oral solid form that is used in most of cases. Oral administration is the most simple, has a lower price, but is associated with a higher rate of side effects in cases with associated gastro-intestinal disorders [13]. Despite simple administration, the oral form of some drugs can determine from minor to major side effects in certain medical conditions (patients with liver, kidney diseases, gastro-intestinal disturbances) or associated harmful habits (alcohol abuse). Actually used anti-TB standard regimens, established according to WHO recommendations are associated with a variable rate of adverse drug reactions (10–15%) diminishing their effectiveness, due to treatment individualization according to clinical and laboratory tolerance [14]. In most cases

the treatment does not show significant (major) adverse drug effects. Clinical monitoring of the treatment is essential for recognizing adverse drug effects [9]. As well as, it permits the prompt and correct management of disturbances appeared due to the TB treatment. Minor side effects (jaundice, nausea, vomiting) permit the continuation of TB treatment with an associated symptomatic treatment. If the patient develops a major side-effect, the responsible drug is stopped and the patient is referred to a specialized health care facility for further management [14]. The most frequent major side effect of the anti-TB drugs is skin rash (itchy rash) that can be developed by any drug: isoniazid, rifampicin, pyrazinamide, or streptomycine. Jaundice (without laboratory evidence of hepatitis) and toxic hepatitis can be induced by isoniazid, rifampicin, or pyrazinamide [14]. Drug-induced hepatotoxicity appears more often in multi-drug TB regimens [13]. The single formulated isoniazid - rifampicin form reports more numerous side effects than the form with one agent used alone [13]. The risk of drug-induced hepatitis is increased by the associated gastrointestinal disorders, liver and kidney diseases, alcohol abuse, and wrong diet [13]. As well as, confusion and nervous impairment can indicate drug-induced acute liver failure, if it is associated with jaundice. The development of acute renal failure, purpura, as major side effects and nausea and abdominal pain, distinguished as minor side effects permits to suspect the involvement of rifampicin in adverse drug reaction [14]. For the detection of the drug which induced hepatotoxic effects, all anti-TB drugs must be stopped, and then reintroduced one by one, at lower dosage till the establishment of the clinical and laboratory tolerance [9]. The mechanism of liver injury is the induction of cytochrome P450 enzyme by isoniazid and/or rifampicin, which increases the quantity of toxic metabolite formed by another drug. In addition to this, rifampicin impairs bilirubin uptake, resulting in elevated bilirubin levels without elevation of transaminases [13]. For clear reasons, patients with hepatobiliary and pancreatic disorders have an increased susceptibility to develop drug-induced injury that permits the individualization of the standard regimen. Individualization of standard regimens determines reducing of dosage, increasing of treatment duration that impairs the efficacy and predisposes to non-adherent patient's behavior [10]. Spectacular, in some cases the anti-TB treatment can cause the enlargement of lung inflammation and progression of parenchymal destructions [6]. Such side effects are probably due to the development of hypersensitivity to mycobacterial antigens and development of immune disturbances, during the first weeks of the treatment [6].

For the treatment of drug-resistant tuberculosis are used second line anti-TB drugs. It requires extensive chemotherapy for two years, shows a higher rate of side effects, and a lower effectiveness. Intensive phase lasts 6 months and requires injected drugs, such as aminoglycosydes and injected fluoroquinolones [14]. Only streptomycin, the component of aminoglycoside class is used in injected form for the treatment of drug-susceptible tuberculosis in certain conditions (children less than 7 years old, disseminated TB), other aminoglycosides (kanamycin and amikacin) are used in the treatment of multidrug-resistant TB. Fluoroquinolones expose high bactericidal activity, used in oral, as well as in injected form in the frame of standard regimens of multidrug-resistant TB and poli-resistant TB [14].

Despite important financial resources involved, the treatment effectiveness in Eastern European States is lower than the European average [2, 8, 10]. Due to this, two injected forms of first – line anti-TB drugs: isoniazid and rifampicin are currently in the course of implementation for the treatment of susceptible TB in the intensive phase performed in hospital conditions. According to the published data, average of maximum concentration of 450 – 600 mg of intravenous injected rifampicin is 22,9 ±2,3 μg/ml, that is 2,5 times higher than the same dose administrated orally 8,9 ±1,3 μg/ ml [7]. As well as, the minimal inhibitory concentration of injected rifampicin is 10 times lower than the oral form (0,03 and respectively 0,3 μg/ml). Considering all scientific review data, it was identified a limited number of studies, exposing the comparative rate of effectiveness and tolerability of first-line injected and oral drugs in the treatment of TB in cases with associated gastro-intestinal disorders.

Aim of the study represented the assessment of treatment efficacy of injected forms of isoniazid and rifampicin at patients with hepatobiliary and pancreatic comorbidities.

Material and methods

A prospective, descriptive, case-control study was realized including 60 new pulmonary infiltrative drug-susceptible cases, with hepatobiliary and pancreatic comorbidities. The study was performed during the period 1.1.2013 – 1.1.2014. Patients were hospitalized in the Chernavtsy Regional Clinical Phtysiopneumological Dispensary. All selected patients were microscopically positive for acid fast bacilli and were treated according to the established new case category. Patients were distributed in a study group, composed of 30 cases treated with oral forms of isoniazid and rifampicin and the control group, composed of 30 cases treated with injected forms of first-line anti-TB drugs (isoniazid and rifampicin). The rest of associated first-line anti-TB drugs (pyrazinamide 2000 mg and ethambutol 1200 mg) were used in oral form. First-line injected drugs were rifampicin (Ріфонат, «Юрія-Фарм» [Rifonat, «Uriya-Pharm»], Ukraine) 30 mg/ml (600 mg) solved in 100 ml of physiological solution of NaCl and injected intravenous; isoniazid (Бітуб, «Юрія-Фарм», [Bitub, «Uriya-Pharm»], Ukraine) 100 mg/ml (300 mg) solved in 100 ml of physiological solution of NaCl and injected intravenous. General established results: men vs women rate was 3/1, with predominance of men in both groups and a medium age of patients was established 39,6 ± 1,3 years old in SG and 38,7± 1,6 years old in CG. So, according to age and sex distribution, the patients were similarly distributed, that permitted a comparable assessment of selected groups. Hepatobiliary and pancreatic disorders were diagnosed using abdominal echography and liver functional tests: serum albumin, bilirubin (direct and indirect), transaminases (ALT, AST), serum creatinine and urea, timol test. The level of endogenous intoxication was

appreciated according to Intoxication Leucocytaire Index (ILI) Kalf-Kalif (1) and Leucocytaire Shift Yabluchianskii Index (LSYI) (2), using the formulas [1, 5]:

ILI Kalf-Kalif = (4M+3Y+2P+S)*(P+1)/Ly+M+E+B (1)

Normal value = 0,3-1,5 Conventional Units (c.u.).

LSYI = E+B+P+S/limphocytes +monocytes (2)

Where: M – monocytes, Y – young neutrophyles, P – plasmocytes, S – segmented neutrophyles, Ly – lymphocytes, E – eosinophyles, B – basophyles. Normal value = 1,5 – 2,2 Conventional Units (c.u.).

Hematological Index of Intoxication (HII) was calculated according to the formula (3) [4]:

HII = ILI * KESR *KL (3)

Where KESR is the correctional coefficient calculated according to erythrocyte sedimentation rate: KESR = 1, if the ESR is < 5 mm/hour, KESR increases by 0,1 unit for each 5 mm/hour if the ESR is between 5 mm/hour and 30 mm/hour, increases by 0,2 unit for the each 5 mm/hour if the ESR is above 30 mm/hour. KL is the correctional coefficient calculated according to leucocytes quantity. If the leucocytes quantity is till 5 * 106/ml the KL is 1 unit and increases by 0,1 unit if the leucocytes quantity is more than 8 * 106/ml.

Lymphocytes Index was approved as being the report of lymphocytes to neutrophyles: LyI=Ly/N; Normal value = 0,5-0,65 Conventional Units (c.u.).

For statistical assessment were used the methods of: comparision, synthesis and discriminant analysis. Microsoft Excel XP and SPSS were used for performing quantitative and qualitative assessment. The degree of conclusion was established to be <0,05.

Results and discussion

Clinical efficacy of injected/oral forms of first-line anti-Tb drugs isoniazid and RIF was assessed after 2 months of treatment according to specially developed symptomatology scale of intoxication syndrom (included such clinical signs: asthenia, anorexia, loss of weight, underweight/cachexia, fever/subfebril temperature, night sweats) and bronchopulmonary scale (included: cough, expectorations, hemoptysis, dyspneea grade according to MRC scale, thoracic pain). The clinical expressiveness was distributed in levels: high, moderate, low and light. It was established that clinical state evaluated through intoxication symptomatology of patients with pulmonary TB and hepatobiliary/pancreatic comorbidities at the end of intesnive phase was better in CG than in SG (table 1). As well as, the bronchopulmonary symptomatology was less expressed in the same group after 60 days of intensive therapy.

Despite a non-significant difference of endogenous intoxication biomarkers between groups of the patients at the onset of the study, the specific treatment changed significantly their state. So, at the end of intensive phase of the treatment, the intoxication index ILI K-K was lower in CG. The rest of indices (HII and LSYI) increased in the SG due to more important immune disturbances developed at those patients (table 2).

Table 1

Expressiveness of the clinical state at the end of intensive phase of TB treatment

Index	Intoxication sdr		Bronchpulmonary sdr	
	SG (n=30),%	CG (n=30), %	SG (n=30), %	CG (n=30), %
Light	56,7	73,3*	50	80*
Low	33,3	26,7	36,7	13,3*
Moderate	10	-	10	6,7
High	-	-	3,3	-
Average t°C	37,4±1,1	37,1±0,4		

Legend: * - statistical difference between SG and CG, n – number of cases.

Radiological dynamics under the influence of different forms of anti-TB drugs and duration (60, 90, 120 days of intensive phase) showed a more evident difference between groups of patients. So, the injected first-line drugs (RIF and HIN) established a conclusive positive dynamics (resorbtion of parenchimal infiltrates, reduction of lung tissue destructions) in CG than in SG after 2 and 3 months of the treatment (table 3).

Table 2

Comparative expressiveness of the endogenous intoxication biomarkers

Index	Sample group (n=20) M±m	Study group (n=30) M±m		Control group (n=30) M±m	
		1	2	1	2
ILI K-K c.u.	1,3±0,5	1,6±0,05	1,8±0,07	1,55±0,07	1,5±0,05*
HII c.u.	1,9±0,46	2,1±0,06	2,99±0,07#	2,13±0,07	2,3 ±0,07*
LSYI c.u.	1,8±0,05	2,1±0,06	2,83±0,05#	1,95±0,05	2,1±0,05*
LyI c.u.	0,6±0,76	0,55±0,06	0,38±0,05	0,46±0,06	0,43±0,05

Legend: ILI K-K – Intoxication Leucocytaire Index Kalf-Kalif, HII – Hematological Index of Intoxication.
LSI – Leucocytaire Shift Index M.I.Yabluchyanskiy, LyI – Lymphocytes Index.
Statistical difference between the index before (1) and at the end (2) of the intensive phase of the treatment within the group.
* – Statistical difference between SG and CG, sample group – group of healthy individuals.

Table 3

Radiological evolution under different forms and duration of TB treatment

Groups	60 days (n=60)		90 days (n=31)		120 days (n=6)	
	Positive	Negative	Positive	Negative	Positive	Negative
	%	%	%	%	%	%
Study group	23,3	3,3	50	21,4	50	25
Control group	47,3*	13,3*	72,7*	45,4*	100	100

Legend: * - statistical difference between SG and CG, n – number of cases.

Table 4

Microbiological dynamics under different forms and duration of TB treatment

Groups	60 days (n=60)	90 days (n=31)	120 days (n=6)	Treatment failure
	%	%	%	%
Study group	36,7	73,7	75	6,7
Control group	60*	91*	100	-

Legend: * – statistical difference between SG and CG, n – number of cases.

Table 5

Biochemical dynamics under different forms and duration of TB treatment (M±m)

Biochemical Indices	Groups	1	2
Albumine (g/)l	SG	72,1±0,59	64,8±0,41
	CG	72,4±0,81	71,7±0,67*
Bilirubine (μmol/l)	SG	15,1±0,46	20,3±0,91#
	CG	14,9±0,44	16,8±0,48
ASAT (mmol/l)	SG	0,41±0,015	0,58±0,016#
	CG	0,40±0,011	0,45±0,013
ALAT (mmol/l)	SG	0,48±0,014	0,63±0,019
	CG	0,45±0,012	0,51±0,018
Urea (mmol/l	SG	5,2±0,22	5,4±0,11
	CG	5,1±0,18	5,2±0,15
Creatinine (kmol/l)	SG	83,5±0,85	91,8±1,23
	CG	81,4±0,53	89,1±1,02
Timol test (c.u.)	SG	3,45±0,22	5,10±0,21#
	CG	3,7±0,29	4,31±0,32*#

Legend: # statistical difference between the index before (1) and at the end (2) of the intensive phase of the treatment within the group, * – statistical difference between SG and CG.

Microbiological assessment, through smear microscopy is essential tool for the treatment monitoring according to DOTS strategy. So, a conclusive difference between the groups was obtained at the end of 2nd and 3rd months of treatment, with a higher microbiological convertion in CG than in SG (table 4). After 3 months of intensive phase, treatment failure was established at 6,7% of patients of SG.

Impact on the general state and laboratory tolerance of TB-drugs used by different ways (injected or orally) at patients with hepato-biliary and pancreatic comorbidities was assessed through serological indices of albumine, bilirubine, transaminases, urea, creatinine and timol reaction. No differences were assessed before starting the treatment.

At the end of the intensive phase a higher level of albumine was established in CG. Timol test established a more elevated result in SG than in CG and indicated a higher drug-induced hepatotoxicity of oraly adminstrated TB drugs. The established fact was proved by the conclusive elevation of bilirubine and transaminases in SG at the end of intensive phase. In CG elevation of serological biomarkers was established, but the statistical threshold was not achieved.

Imagistic exploration of the hepatobiliary system established increasing of the right liver lobe at 80,0% of all investigated patients by 0.7 ± 0,71 mm and resulted in a total length 15,1 ± 1,21 mm, the left liver lobe increased at 73,3% cases by 0,82 ± 0,12 mm with a total length 11,2 ± 2,7 mm, the signs of diffuse liver damage, expressed as hyperechogenic changes and increase of the portal vein size were identified at 68,3% cases.

Conclusions

Assessing the differences between the clinical and laboratory tolerance of TB drugs according to the way of administration, it was proved the importance of individualization of the standard treatment at patients with hepatobiliary and pancreatic disorders by intravenous use of isoniazid and rifampicin in intensive phase, for improving the quality of the TB treatment.

The clinical improvement of the patient's general state under the influence of intravenous use of isoniazid and rifampicin was confirmed by a lower expressiveness of intoxication and bronchopulmonary syndroms, as well as by a better radiological dynamics and higher rate of microscopic convertion at the end of intensive phase of the TB-treatment.

Biochemical disturbances due to TB treatment was less evident at the patients treated with intravenous isoniazid and rifampicin, confirmed by a better rehabilitation of mathematic indices of endogenous intoxication.

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